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09/780,035	02/09/2001	Tariq Ghayer	BBI-149	8433

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EXAMINER
ROARK, JESSICA H

ART UNIT	PAPER NUMBER
1644	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/780,035	Applicant(s) GHAYER ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *39-43 and 47-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38 and 44-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The Examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Jessica Roark, Art Unit 1644, Technology 1600.

2. Applicant's amendment, filed 7/27/01 (Paper No. 5), is again acknowledged.
Claims 39, 44, 54, 56 and 58 have been amended.
Claims 1-60 *are pending.*

3. Applicant's election with traverse of Group IV (claims 1-38 and 44-46) with a species election of a human antibody and CDRs specified by SEQ ID NOS:9-14 in Paper No.9 is acknowledged.

The traversal is on the grounds that claim 1 is a generic claim and that the examination of Groups II-IV as one Group would not present an undue burden on the Examiner based upon the classification of the Groups in Class 530.

This is not found persuasive for the reasons set forth in Paper No. 7. In particular it is noted that the compounds of Groups II-IV differ in their structures, as evidenced by their classification in different subclasses of Class 530. Thus contrary to Applicant's assertions, the searches are not co-extensive.

The requirement is still deemed proper and is therefore made FINAL.

Claims 39-43 and 47-60 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Because a human antibody comprising CDRs specified by SEQ ID NOS:9-14 and that binds an epitope of human IL-18 appears to be free of the art, the search has been extended to encompass the various species recited in claims 22-38.

Claims 1-38 and 44-46 *are under consideration in the instant application.*

4. Sequence compliance: The instant application appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

5. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, provisional application 60/181,608 to which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-3, 11-15 and 22-38 of this application.

Although 60/181,608 provides an adequate written description of the IL-18 epitope defined by instant SEQ ID NO:1 and human monoclonal antibodies to this IL-18 epitope or intact IL-18; the priority document does not appear to support the IL-18 epitopes of SEQ ID NOS:3 or 33 (claims 11-15); nor does it support antibodies comprising at least one CDR or individual antibody species (claims 22-38). Finally, the 60/181,608 document does not appear to contemplate compounds other than antibodies (claims 1-3).

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

It is suggested that Applicant delete the phrase "AND METHODS OF MAKING AND USING".

7. The formal drawings submitted 2/9/01 have been approved by the Draftsman.

8. Applicant's IDS, filed 12/12/01 (Paper No. 8), is acknowledged.

9. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

10. Claim 2 is objected to for the non-elected embodiments recited in this claim.

11. Claim 46 is objected to because of the following informalities:
in the third line, it appears a comma has been omitted following "methotrexate"; and
there appears to be extraneous text following the period in the fourth line.

Appropriate correction is required.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-3, 11-15 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-3 are ambiguous and unclear as to not only the metes and bounds of the claims, but even as to what is being claimed.

First it is noted that the only amino acid sequence recited in the claim appears to be that of IL-18. However, SEQ ID NOS:67 and 68 do not appear to be related to IL-18. Further, SEQ ID NO:68 is a nucleic acid, rather than amino acid sequence; thus it is lacking antecedent basis within the claim.

It is also unclear as to whether the "portion thereof" refers to the IL-18 sequence, or the compound.

For examination purposes and in light of the restriction requirement, claim 1 will be interpreted as reciting "An antibody or fragment thereof capable of binding human IL-18 or a portion of human IL-18".

B) Claims 11-15 are indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of ..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y).

C) Claim 46 is ambiguous in that it is unclear what additional agents are recited in the claim. In particular, the instant claim language encompasses antibodies to IL-12, antibodies to methotrexate, etc. If only the only antibody intended is one to IL-12, the claim should be re-written to clearly indicate this.

D) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-3 and 22-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

a) Claims 1-3 recite "a compound capable of binding a human IL-18 amino acid sequence" as part of the invention.

However, Applicant has disclosed only compounds capable of binding human IL-18 that are antibodies (or antigen-binding fragments of antibodies). Thus Applicant has disclosed a single species of "compound capable of binding human IL-18". The genus of compounds that are capable of binding human IL-18 is extensive, encompassing many structurally diverse compounds such as small molecules, carbohydrates, IL-18 receptors and fragments thereof, viral proteins, etc. Thus Applicant does not appear to have described a sufficient number of representative species for the extensive genus claimed.

Neither does Applicant appear to have provided any correlation between a particular structure of the genus of compounds and the recited function of binding human IL-18.

Consequently, the ordinary artisan would not recognize Applicant to be in possession of the instant invention as broadly claimed.

b) Claims 22-38 recite in various forms an antibody or antigen-binding portion thereof comprising "at least one variable region CDR" or "a CDR domain selected from the group consisting of" or variable regions comprising SEQ ID NOS that are individual CDR domains. Thus claims 22-38 recite in some form "an antibody in which fewer than all CDRs are defined".

Applicant has disclosed antibodies in which all three CDRs of the heavy chain variable region and all three CDRs of the light chain variable region are defined. Although a limited number of changes are made to individual CDRs, these changes are always made in the context of a total of six CDRs in any given antibody. Applicant does not appear to describe any antibodies in which fewer than six CDRs are defined and which have the function of binding IL-18 or a peptide comprising an epitope of IL-18.

Thus the minimal structure which provides the function of IL-18 or IL-18 epitope binding appears to include six CDRs (three in the heavy chain variable region and three in the light chain variable region).

Further, Applicant appears to acknowledge that all six CDRs are required for the recited function in the response filed 3/28/02 (see the comments on pages 4-5 regarding election of species).

Thus the ordinary artisan would not recognize Applicant to be in possession of an antibody or antigen-binding fragment thereof that binds human IL-18 or an epitope of human IL-18, unless all six CDRs are defined.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

16. Claims 1-3 and 22-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies and antigen-binding fragments thereof in which the three CDRs in the heavy chain variable region and the three CDRs in the light chain variable region are all defined by a single antibody which binds the relevant antigen (human IL-18 or a peptide epitope thereof) and for mutants of these antibodies in which a limited number of defined changes are made in one or more CDRs; does not reasonably provide enablement for antibodies and antigen-binding fragments thereof that comprise less than three heavy chain CDRs and three light chain CDRs defined by the amino acid sequence of a parental antibody that binds the same antigen, or for other compounds that bind human IL-18. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficiently enabling description of the claimed invention.

a) Claims 1-3 recite "a compound capable of binding a human IL-18 amino acid sequence" as part of the invention.

The breadth of the instant claims encompass any natural or synthetic compound with the function of binding human IL-18 or a portion thereof. Applicant has provided working examples only of antibodies and antigen-binding fragments thereof that bind human IL-18 or peptide fragments of human IL-18.

However, while the state of the art recognized that antibodies and the natural IL-18 receptor could bind IL-18, and that antibodies could bind peptide fragments of IL-18; the state of the art also recognized that it was highly unpredictable as to which other natural or synthetic compounds would bind IL-18 or peptide fragments thereof, as evidenced by the paucity of non-antibody/non-receptor inhibitors of cytokines such as IL-18 in the literature. Given the absence of guidance in the specification as filed as to the nature of these other compounds and the failure of the state of the art to recognize that compounds other than antibodies and forms of the natural receptor could be used to bind IL-18 (or other cytokines); it would require undue experimentation of the skilled artisan to make other non-antibody or non-receptor compounds which could bind IL-18 and be used in methods of inhibiting IL-18 function. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

b) Claims 22-38 recite in various forms an antibody or antigen-binding portion thereof comprising "at least one variable region CDR" or "a CDR domain selected from the group consisting of" or variable regions comprising SEQ ID NOS that are individual CDR domains. Thus claims 22-38 recite in some form "an antibody in which fewer than all CDRs are defined".

The breadth of the instant claims encompass antibodies or antigen-binding fragments thereof in which fewer than all of the six CDRs found in the heavy plus light chain pair that forms the binding region of a referenced antibody are defined.

As noted supra, Applicant has disclosed antibodies in which all three CDRs of the heavy chain variable region and all three CDRs of the light chain variable region are defined. Although a limited number of changes are made to individual CDRs (e.g., the mutations described in Table 12), these changes are always made in the context of a total of six CDRs in any given antibody derived from a reference antibody that binds IL-18 or an epitope thereof.

The state of the art recognized that all three CDRs of the heavy chain variable region and all three CDRs of the light chain variable region were important for determining the ability of the antibody to bind antigen. For example, Bendig (Methods: A Companion to Methods in Enzymology 1995; 8:83-93) reviews that the general strategy for "humanizing" antibodies involves the substitution of all six CDRs from a rodent antibody that binds an antigen of interest, and that all six CDRs are involved in antigen binding (see entire document, but especially Figures 1-3). While the instant antibodies are fully human, the same considerations apply to the genus of human antibodies defined only based upon CDR sequences.

Thus the state of the art recognized that it would be highly unpredictable that an antibody comprising less than all six CDRs from an antibody with a desired specificity would bind the same antigen. Thus the minimal structure which provides the function of IL-18 or IL-18 epitope binding appears to include six CDRs (three in the heavy chain variable region and three in the light chain variable region) from the same antibody.

Further, Applicant appears to acknowledge that all six CDRs are required for the recited function in the response filed 3/28/02 (see the comments on pages 4-5 regarding election of species).

In addition, the skilled artisan recognized that single CDRs with the same amino acid sequence could be found in antibodies with diverse specificities. In particular, antibodies which have not yet undergone affinity maturation may still utilize germline heavy and light chain sequences. Between antibodies utilizing the same germline heavy or light chain gene the skilled artisan would expect to find that one or more of the heavy and/or light chain CDRs were the same as that of an antibody with a different specificity, particularly CDRs 1and 2 which are germline encoded completely in the variable region. However, the same CDR may also occur in antibodies having somatic mutations that bind different antigens.

For example, an anti-tumor antibody taught by Garen et al. (US Pat. No. 6,140,470) has the heavy chain set forth in SEQ ID NO:32 of the Garen et al. patent. The heavy chain of SEQ ID NO:32 has the same CDR1 and CDR2 sequences as the heavy chain of the instant anti-IL-18 antibody LT28 (instant SEQ ID NO:28, comprising CDR1 defined by SEQ ID NO:20 and CDR2 defined by SEQ ID NO:21). Thus it would be highly unpredictable that an antibody comprised of fewer than all six CDRs (three CDRs defined in the heavy chain variable region and three CDRs defined in the light chain variable region) of a particular reference antibody would have the same specificity as the reference antibody.

The specification as filed provides no working examples showing that fewer than all six CDRs are required for binding to IL-18 or an epitope thereof. Neither does the specification appear to provide sufficient guidance as to which subsets of CDRs could be used in an antibody comprising less than all six CDRs from an antibody having IL-18 binding specificity and still maintain IL-18 binding. Without sufficient guidance, it would require undue experimentation of the skilled artisan to make antibodies or antigen-binding fragments thereof which could bind IL-18 and be used in methods of inhibiting IL-18 function that comprised fewer than all six CDRs from a parental antibody that bound IL-18.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Given the recognized unpredictable nature of making antibodies with a desired specificity having fewer than all six CDRs from a reference antibody and the lack of sufficient guidance provided in the specification; the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. The rejections under the subsections of 35 USC 102 have been applied as appropriate based upon the effective filing date of the individual claims. Please see the discussion of priority supra.

Also note that given the ambiguity associated with the language of instant claim 1, claim has been interpreted as indicated supra under the rejections under 35 USC 112, second paragraph.

19. Claims 1-2, 11-12 and 14-15 are rejected under 35 U.S.C. 102(a) as being anticipated by Ho et al. (WO00/56771 #A2, 28 Sept 2000, see entire document)

Ho et al. teach neutralizing monoclonal antibodies capable of binding human IL-18 (see entire document, e.g., summarized on pages 27-28). IL-18 inherently comprises the amino acid sequences of SEQ ID NO:3 and SEQ ID NO:33, since SEQ ID NO:3 and SEQ ID NO:33 are subsequences of human IL-18. Thus the antibody of Ho et al. binds an epitope of IL-18 comprising these sequences.

Ho et al. also teach the production of humanized (i.e., recombinant) anti-IL-18 monoclonal antibodies (e.g., pages 16-20 and title).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the neutralizing antibody to human IL-18 and the human IL-18 molecule.

The reference teachings thus anticipate the instant claimed invention.

20. Claims 16-21 are rejected under 35 U.S.C. 102(a) as being anticipated by Yoshihiro et al. (EP 0 974 600 A2, IDS #A1, 26 Jan 2000, see entire document).

Yoshihiro et al. teach antibodies capable of binding human IL-18 (See entire document, e.g., paragraphs 45-49 on pages 9-10).

Although Yoshihiro et al. do not test the k_{off} rate or determine the IC_{50} with which the antibody inhibits human IL-18 activity, as recited in instant claims 16-21, Yoshihiro et al. do teach that the anti-IL-18 antibody can neutralize the activity of IL-18 (e.g., paragraphs 60-61). The specific functional properties recited in instant claims 16-21 would be inherent properties of a neutralizing antibody to human IL-18.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the neutralizing antibody to human IL-18.

The reference teachings thus anticipate the instant claimed invention.

21. Claims 1-2, 11-12 and 14-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoshihiro et al. (EP 0 974 600 A2, IDS #A1, 26 Jan 2000, see entire document)

Yoshihiro et al. teach monoclonal antibodies capable of binding human IL-18 (See entire document, e.g., paragraphs 45-49 on pages 9-10). IL-18 inherently comprises the amino acid sequences of SEQ ID NO:3 and SEQ ID NO:33, since SEQ ID NO:3 and SEQ ID NO:33 are subsequences of human IL-18. Thus the antibody of Yoshihiro et al. binds an epitope of IL-18 comprising these sequences.

Yoshihiro et al. also teach that the anti-IL-18 antibody can neutralize the activity of IL-18 (e.g., paragraphs 60-61).

Yoshihiro et al. also clone the DNA of an anti-IL-18 monoclonal antibody and produce a recombinant monoclonal antibody (e.g., paragraphs 50-63).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the neutralizing antibody to human IL-18 and the human IL-18 molecule.

The reference teachings thus anticipate the instant claimed invention.

22. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

23. Claims 1-24 and 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kucherlapati et al. (US Pat No. 6,075,181) and Dinarello et al. (J. Leukoc. Biol. 1998; 63:658-664, IDS #A4).

Kucherlapati et al. teach a method of producing fully human monoclonal antibodies to any protein of interest, but especially cytokines, by using the protein to immunize mice which express human antibody genes (see entire document, but especially columns 8-9. Kucherlapati et al. teach that fully human monoclonal antibodies are highly advantageous compared to rodent antibodies or even humanized antibodies for therapeutic applications, because administration of human antibodies to humans avoids the undesired immune responses elicited by administering non-human antibodies to humans (see column 8, especially lines 21-41).

Kucherlapati et al. also teach that the human antibody genes can be cloned and used to produce recombinant, fully human, monoclonal antibodies, e.g., for phage display libraries (e.g., columns 6-7). Kucherlapati et al. teach that such recombinant human antibodies offer the advantage that phage libraries can be screened for selection of antibodies with the highest affinity to the antigen of interest, or can be manipulated to increase the affinity of the antibody for the antigen (e.g., column 7, especially the comment at lines 58-65).

Kucherlapati et al. do not teach human antibodies to IL-18.

Dinarello et al. teach that human IL-18 had been cloned and produced recombinantly (see e.g. page 659 "Molecular cloning of IGIF"). Dinarello et al. review that IL-18 initiates the Th1 inflammatory cytokine cascade, leading to the production of later cytokine mediators such as TNF-α, IL-1 and IL-8, and that antibodies to IL-18 can inhibit the in vivo production of other cytokines such as TNF-α (e.g. page 660, right column). Dinarello et al. note that given what is known about the role of cytokines such as TNF-α, IL-1 and IL-8 that are induced by IL-18 in human disease such as rheumatoid arthritis and Crohn's Disease; that preventing the activity of IL-18 which induces these other cytokines is a sensible clinical strategy (e.g., page 662 "What is the clinical importance of the pro-inflammatory cytokine IL-18?). Dinarello et al. also note in this discussion of the clinical importance of inhibiting IL-18 activity that neutralizing anti-IL-18 antibodies are a therapeutic option for inhibiting IL-18 activity.

Therefore, it would have been obvious to the ordinary artisan at the time the invention was made to produce human antibodies to human IL-18 that were capable of neutralizing the activity of IL-18. Recombinant IL-18 was known in the art at the time the invention was made, as taught by Dinarello et al. Kucherlapati et al. provide a method of producing fully human antibodies to human cytokines. Thus the ordinary artisan at the time the invention was made would have had a reasonable expectation that, given the availability of recombinant human IL-18, fully human antibodies to human IL-18 could be produced using the method of Kucherlapati et al.

The ordinary artisan at the time the invention was made would have been motivated to produce fully human monoclonal antibodies that could bind to and neutralize human IL-18 in order to provide a therapeutic reagent that could be administered to humans without eliciting the undesirable immune responses associated with the administration of rodent or even humanized rodent antibodies, as taught by Kucherlapati et al. The desirability of neutralizing antibodies to human IL-18 is clearly taught by Dinarello et al.

Further, the ordinary artisan at the time the invention was made would have been motivated to provide recombinant forms of the fully human antibodies so that the binding affinity and ability of the antibody to neutralize human IL-18 could be improved by successive rounds of manipulation and screening of phage display libraries of the human anit-IL-18 monoclonal antibodies. Although monoclonal antibodies typically have k_{off} rate constants as measured by surface plasmon resonance and inhibition activity with an IC_{50} in the ranges recited, using the affinity maturation approach as taught by Kucherlapati et al would have ensured that the ordinary artisan would have obtained human antibodies that bound human IL-18 and had k_{off} rate constants of $1x10^{-6}s^{-1}$ and IC_{50} values of $1x10^{-11}M$. Further, the affinity modifications taught by Kucherlapati et al. would have resulted in at least one amino acid substitution or insertion that improves the IL-18 binding as compared to the original antibody. Any human anti-human IL-18 antibody would of necessity possess at least one variable region CDR domain capable of binding an epitope of human IL-18, and would bind an epitope of human IL-18 comprising SEQ ID NOS:3 or 33, since SEQ ID NOS:3 and 33 are each subsequences of human IL-18.

Finally, given that the ordinary artisan would have been motivated to provide human monoclonal antibodies to human IL-18 because of their therapeutic potential in inflammatory diseases, as taught by Dinarello et al.; the ordinary artisan would have clearly been motivated to formulate the human anti-human IL-18 antibody in a pharmaceutical composition. The addition of at least one additional therapeutic agent already shown to have some efficacy against these inflammatory diseases, e.g., the addition of methotrexate or anti-TNFα for the treatment of rheumatoid arthritis, would have also been an obvious combination at the time the invention was made to provide a more efficacious therapeutic composition. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

24. No claim is allowed.

25. It is noted that claims drawn to the following antibodies would appear to be free of the art:
1) an antibody comprising the heavy chain variable region defined by SEQ ID NO:18 and the light chain variable region defined by SEQ ID NO:19;
2) an antibody comprising the heavy chain variable region defined by SEQ ID NO:28 and the light chain variable region defined by SEQ ID NO:29;
3) an antibody comprising a heavy chain variable region in which the CDRs are defined by SEQ ID NOS:9-11 and a light chain variable region in which the CDRs are defined by SEQ ID NOS:12-14; and
4) an antibody comprising a heavy chain variable region in which the CDRs are defined by SEQ ID NOS:20-22 and a light chain variable region in which the CDRs are defined by SEQ ID NOS:23-25.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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June 24, 2002

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6/24/02